

In re Application of:
Foster et al.
Application No.: 10/017,135
Filed: December 7, 2001
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PATENT
Atty Docket No.: HILLS1100

Remarks

Claims 1-20, 28 and 30-39 are pending in the present application. By the present communication, no claims have been amended; claims 36-39 have been added; and no claims have been canceled. Support for the amendments may be found throughout the specification and claims as filed. Accordingly, upon entry of the present amendment, claims 1-20, 28 and 30-39 will be under consideration.

Applicants thank Examiner Sheikh for the telephonic interview of June 19, 2008. Applicants respectfully request that in the event the Examiner intends to maintain a further rejection after review and consideration of the amendments and arguments submitted herein, the rejection be a non-final rejection, in particular, given the issues raised in the interview. Applicants also respectfully ask that all claims be examined.

Rejections under 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 1-20, 28, and 30-35 under 35 U.S.C. §103(a) as allegedly being obvious over Debendetti et al. (U.S. Patent No. 6,063,910) in view of Merrified et al. (WO 00/37169).

The recent U.S. Supreme Court decision in *KSR International v. Teleflex Inc.* (82 USPQ 2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

In maintaining the rejection of claims 1-20 based upon obviousness, the Examiner alleges the previous declaration of Dr. Linda Sze Tu, submitted under 37 C.F.R. §1.132 along with the Response to the Office Action filed October 25, 2007, is insufficient to overcome the rejection of

the claims because the showing is not commensurate in scope with the instant claims. The Examiner has identified the following issues in relation to the previously filed declaration:

- (i) with regard to the Ting et al. reference cited in the declaration, demonstrating a non-linear dependence between the solubility of naproxen and co-solvent concentration, the Examiner alleges that non-linear behavior is not necessarily unpredictable if a proper model can be found;
- (ii) with regard to the Hutchenson et al. reference cited in the declaration, demonstrating the state of art at the effective priority date of the application (December 7, 2000), the Examiner alleges that Hutchenson et al. may not have remained an accurate description of the state of the art at the effective priority date of the application because Hutchenson et al. was published in 1995;
- (iii) with regard to the Jouyban et al. reference cited in the declaration, the Examiner appears to allege that because the reference shows a global average absolute relative deviation (AARD) of 12.6%, supercritical fluid processes are predictable; and
- (iv) notwithstanding the assertions of Dr. Linda Sze Tu in the declaration that at least two changes are required to the most relevant examples of Debendetti et al. to arrive at the claimed invention, the Examiner maintains that only one change is required.

Applicants will address each issue in turn and respectfully request reconsideration of the instant claims in light of the previously filed declaration by Dr. Sze Tu of October 25, 2007, the supplemental declaration of Dr. Sze Tu submitted herewith as Exhibit A, and the following arguments.

I. Ting et al.

Applicants respectfully submit that the Examiner has misconstrued the declaration with respect to Ting et al. The declaration highlighted that research performed prior to Ting et al. had revealed a linear dependence between co-solvent composition and the solubility of organic compounds in supercritical ethane (see page 2, line 8 of the declaration filed October 25, 2007).

In contrast, the experiments of Ting et al. demonstrated a non-linear dependence between the solubility of naproxen and co-solvent composition. Based on the contradictory teachings of the art (prior to Ting et al.) and Ting et al., it would be impossible for one of skill in the art to predict whether the solubility of a compound in a supercritical fluid composition will demonstrate a linear dependence or non-linear dependence. As such, the assertion in the Office Action that non-linear behaviour may be predictable if the proper model may be found is irrelevant since it is impossible to predict whether a linear or non-linear model should be applied to a given supercritical system.

Dismissing certain conclusions reached in the previous declaration by Dr. Sze Tu, filed October 25, 2007, the Office Action fails to present a model that may be used to predict the non-linear behavior of an supercritical fluid (SCF) process of the present invention, but merely states that "non-linear behavior is not necessarily unpredictable if a proper model can be found" (see page 5, third paragraph of the Office Action). Applicants respectfully submit that one of skill in the art would not be motivated to generate such a model based on the teachings of the prior art. Particularly, Debendetti et al. teaches away from the use of aqueous solutions by teaching that they are undesirable (see column 6, lines 29-32). Therefore, clearly one of skill in the art would not be motivated to generate a model including as a variable the use of aqueous solutions, and thus, without such a model, there could be no reasonable expectation of success in practicing the invention.

Additionally, Applicants respectfully direct the Examiner to the previous declaration, filed October 25, 2007, (page 3 lines 9-20) and the supplemental declaration of Dr. Sze Tu, submitted herewith as Exhibit A, discussing the level of knowledge possessed by one of ordinary skill in the art as pertains to the unpredictability of SCF processes. Dr. Sze Tu indicates that determining whether to apply a linear or non-linear model to a given supercritical system, is by no means routine and requires significant effort, even for those of skill in the art (see paragraph 7 of the supplemental declaration). This is in part due to the complexity and unpredictable nature of supercritical systems that results from the high propensity of producing unexpected results by

varying even one of a number of variables (i.e., temperature, concentration of substance, partial pressure, and the like) in a given supercritical system (see paragraph 11 of the supplemental declaration). That is, the variation in one variable may lead to a consequent change in many other variables.

Accordingly, Applicants respectfully submit that it is unreasonable to conclude that one of skill in the art could practice the invention as claimed with a reasonable expectation of success by combining the teachings of Debendetti et al. and Merrified et al. due to the unpredictable nature of SCF processes.

II. Hutchenson et al.

Applicants respectfully submit that Hutchenson et al. accurately represents the state of the art at the effective priority date of the instant application (December 7, 2000). Contrary to the assertion in the Office Action, Applicants respectfully direct the Examiner to Exhibit A which indicates that Dr. Linda Sze Tu believes Hutchenson et al. accurately describes the state of the art at the time of filing of the instant application. Exhibit A also indicates that Dr. Linda Sze Tu was unable to locate any references prior to the effective priority date of the instant application conflicting with the description of the state of the art as presented in the exhibits cited in the previously filed declaration (i.e., Ting et al. and Hutchenson et al.). Accordingly, Applicants respectfully submit that Hutchenson et al. accurately describes the state of the art at the effective priority date of the instant application and characterizes the unpredictability of SCF behavior and the difficulties of adequately and quantitatively predicting such behavior.

Accordingly, Applicants respectfully submit that it is unreasonable to conclude that one of skill in the art could practice the invention as claimed with a reasonable expectation of success by combining the teachings of Debendetti et al. and Merrified et al. due to the unpredictable nature of SCF processes.

III. Jouyban et al.

Applicants respectfully submit that the Examiner has misconstrued the declaration with respect to Jouyban et al. The Office Action alleges that the reference demonstrates a global average absolute relative deviation (AARD) of 12.6% which is within the range of acceptable error and therefore all supercritical fluid (SCF) processes are predictable. Applicants submit that as presented in the prior declaration of Dr. Sze Tu, filed October 25, 2007, Jouyban et al. discloses the ongoing complexities and difficulties of predicting SCF processes.

Applicants note that the publication date of the reference (May 2002) post dates the priority date of the instant application (December 7, 2000) by approximately 18 months. As such, the reference is intended to exemplify that even after the effective priority date of the instant application, ongoing difficulties of predicting SCF processes remained. Jouyban et al. teaches that by altering only one or two parameters of an SCF process (i.e., temperature and the substance being dissolved), a wide range of solubility predictions results (producing AARD's of between 12.6% and 24.8% - the previous examiner selected only the lowest deviation, not the average) in a single system due in part to the complexity of interaction of the various parameters of the process and the phenomenon that varying a single parameter (i.e., temperature) inherently affects other variables of the process.

IV. Required Changes to the Cited References to Arrive at the Present Invention

Applicants respectfully disagree with the contention presented in the Office Action that only one change is being made over the teachings of Debendetti et al., the addition of a modifying agent, in order to arrive at the presently claimed invention. In the declaration previously submitted on October 25, 2007, Dr. Sze Tu indicated that the effect of one change on the outcome of an SCF process would be difficult for one of ordinary skill in the art to predict, and simultaneously introducing a second change in the process would mean that the prediction of the outcome of the process would be almost impossible.

In conclusory fashion, the Office Action indicates that because Debendetti et al. allegedly teaches the use of an aqueous non-gaseous fluid, the predicted outcome involves only one change to be analysed (the addition of a modifying agent). Applicants disagree, and assert that contrary to the aqueous solution of the present claims, the medium used to dissolve the substance as disclosed in Debendetti et al. is substantially an organic fluid (i.e., ethanol) with substantially little water, whereas the aqueous fluid of the present invention includes a non-organic fluid (i.e. water) with relatively little or no organic fluid (i.e. alcohols such as ethanol).

For reasons presented in the Response to the Office Action, filed October 25, 2007 and of record, Applicants reassert that Debendetti et al. fails to disclose the aqueous fluid of the present invention. As taught in Debendetti et al., ethanol is considered by the present specification to be an organic solvent (see paragraph [0014] of the present specification) and is to be avoided in the solution in order to avoid denaturation or degradation of the substance (see [0011] of the present specification). Furthermore, Debendetti et al. fails to teach a fluid that is substantially void of an organic solvent. Rather, Debendetti et al. teach that the fluid must comprise at least one non-aqueous solvent (see column 6, lines 18 to 22) since the invention of Debendetti et al. is useful for hydrophobic substances (see column 2, lines 31 to 40) which have poor solubility in aqueous fluid.

Thus, given that Debendetti et al. fails to disclose the use of an aqueous non-gaseous fluid and the addition of a modifying agent, it must be concluded that at least two changes are being made to the process. Even if one were to assume *arguendo* that the predicted outcome involves only one change to be analysed as asserted in the Office Action (i.e., the addition of a modifying agent), Applicants respectfully submit that the previously filed declaration has been misconstrued by the Examiner. The state of the art (i.e., Ting et al. and Hutcheson et al.) as presented in the declaration previously filed and the supplemental declaration submitted herewith, clearly indicate that the effect of modifying co-solvent composition on the solubility of a compound could not be predicted at the priority date of the instant application. Changing or introducing a modifying agent similarly would have an unpredictable impact.

Furthermore, Applicants submit that modifying one variable will have an effect on all variables of the system as indicated by Dr. Sze Tu in the supplemental declaration (see paragraph 11). Dr. Sze Tu indicates that even if it were possible to reliably predict the effect of the modification of one variable on another, one cannot predict the effect of that modification on all the other variables because it is unpredictable how the modification will affect the overall system. This is mainly due to the complexity and unpredictable nature of supercritical systems that results from the high propensity of producing unexpected results by varying even one of a number of variables (i.e., temperature, concentration of substance, partial pressure, and the like) in a given supercritical system. Therefore, even if one were to modify the process only by including a modifying agent with the anti-solvent one cannot predict the effect of that modification on all the other variables because it is unpredictable how the modification will affect the overall system. Accordingly, one of skill in the art would have no reasonable expectation of practicing the invention as claimed by combining the teachings of the cited art.

In light of the above discussion and both the supplemental declaration (Exhibit A) and previously filed declaration of Dr. Sze Tu, Applicants respectfully submit that the Office Action fails to establish a *prima facie* case of obviousness because the combination does not suggest a reasonable expectation of success to one of skill in the art in practicing the claimed invention by combining the teachings of Debendetti et al. and Merrified et al. Applicants respectfully submit that one of ordinary skill in the art would not have sufficient knowledge to have a reasonable amount of predictability in determining the effects in altering the parameters of such precipitation processes to successfully arrive at the claimed invention.

Dr. Sze Tu's declarations discuss the unpredictability of supercritical fluid behavior and the difficulties of adequately and quantitatively predicting such behavior. As discussed above and throughout the declarations, a number of references from the scientific literature indicate that it is difficult to predict the effects of changes made to dense gas processes. Applicants submit that disparate teachings gathered from the cited art cannot be successfully combined to practice the claimed invention with a reasonable expectation of success due to the unpredictability of SCF

processes. In particular, based on Dr. Sze Tu's declarations and the references cited therein, the state of the art at the time of filing is clearly characterized by a lack of predictability of dense gas processes. For example, Hutchenson et al. stated that predicting SCF behavior was difficult in "even the simplest of systems" and that the difficulty was even more pronounced in more complex systems. Additionally, one of skill in the art cannot predict whether a linear or non-linear model should be applied to a given supercritical system, and specifically, which specific model may be applied. Further, Dr. Sze Tu indicates that it is impossible to predict the effect of a particular modification of an SCF process on all the other variables of the process because it is unpredictable how the modification will affect the overall system.

Applicants respectfully submit that the presently claimed method exhibits unpredictable and unobvious results over the cited art. As indicated in Exhibit A, the Examples of the present application teach the method of the present claims which includes dissolving a substance in an aqueous non-gaseous fluid (i.e. water), substantially free of an organic fluid and supplying a modifying agent with the anti-solvent (see paragraph 12). As indicated in paragraph 13 of Exhibit A and the instant specification, the process employed in the Examples of the present specification produce unexpected results over the teachings of Debendetti et al. For instance, Example 2 of the present application teaches production of insulin solutions having a concentration of 100 mg/mL (see, paragraph [0089]) as compared to Example 2 of Debendetti et al. which teaches an insulin solution of 0.1 mg/mL (see column 9, lines 4 to 5). This higher concentration (by 3 orders of magnitude) in turn leads to higher throughputs and higher yields (see, for instance, example 4 at paragraph [0095] where a yield of 90% is demonstrated). Such high concentrations and resulting yields are contrary to the teachings of Debendetti et al. which teach that water is to be avoided since it lowers the yield (see column 6, lines 28 to 32). Clearly, such a drastic increase in the yield demonstrated by the claimed method is superior and unexpected over the teachings of the cited art.

Additionally, as outlined in the specification of the present application at page 10, lines 1-2, an unexpected and surprising advantage of the subject invention is "[T]he ability to use

aqueous solutions thereby enabling concentrated solutions of material to be processed with minimal risk of deactivation of biological activity.” In the process of the present invention as claimed, contact with organic solvents is minimized, limited only to the time that the solution of the substance (an aqueous solution) mixes with the dense gas. In this way, the potential for protein denaturing is minimized.

With regard to claim 28, Applicants note that the claim includes further elements directed toward the apparatus that exhibit unexpected and surprising advantages over the cited art. In particular, the additional elements of the claim reduce agglomeration and continuous collection of the micronized particles due the configuration of the apparatus. Applicants direct the Examiner to paragraphs [0057], [0058], [0075]-[0076], [0097] and Figure 11 of the specification disclosing the advantages of the claimed configuration including reduced agglomeration and “parallel” collection vessels allowing for continuous collection versus single batch collection.

For the foregoing reasons, Applicants submit that the claimed invention is not obvious over Debendetti et al. in light of Merrified et al. and respectfully request that the rejection of the claims under 35 U.S.C. §103(a) be withdrawn.

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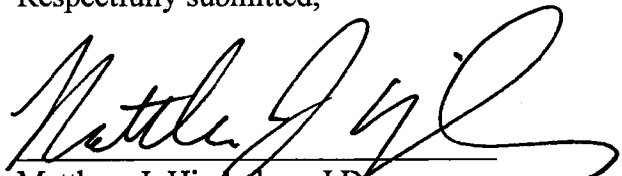
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Conclusion

In summary, for the reasons set forth herein, Applicants submit that the claims clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge the total amount of \$525.00 as payment for the Three-Month Petition for Extension of Time fee for small entity, to Deposit Account No.: 07-1896. No other fees are deemed necessary for the filing of this paper. However, the Commissioner is further authorized to charge any additional fees required, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,



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